This is the peer reviewd version of the followng article:

The dementia-associated APOE ε4 allele is not associated with rapid eye movement sleep behavior disorder / Gan-Or, Z., Montplaisir Jacques, Y., Ross Jay, P., Poirier, J., Warby Simon, C., Arnulf, I., Strong, S., Dauvilliers, Y., Leblond Claire, S., Hu Michele, T.M., Högl, B., Stefani, A., Monaca Christelle, C., De Cock Valérie, C., Boivin, M., Ferini-Strambi, L., Plazzi, G., Antelmi, E., Young, P., Heidbreder, A., et al.. - In: NEUROBIOLOGY OF AGING. - ISSN 0197-4580. - 49:(2017), pp. 218.e13-218.e15. [10.1016/j.neurobiolaging.2016.10.002]

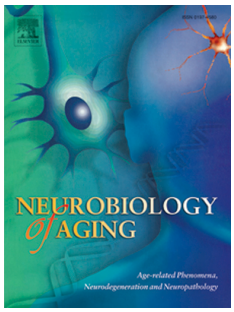
Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

21/11/2026 23:15

(Article begins on next page)

Accepted Manuscript



The dementia-associated *APOE* ε4 allele is not associated with REM sleep behavior disorder

Ziv Gan-Or, MD, PhD, Jacques Y. Montplaisir, MD, PhD, Jay P. Ross, BSc, Judes Poirier, PhD, Simon C. Warby, PhD, Isabelle Arnulf, MD, PhD, Stephanie Strong, BSc, Yves Dauvilliers, MD, PhD, Claire S. Leblond, PhD, Michele T.M. Hu, MBBS, FRCP, PhD, Birgit Högl, MD, Ambra Stefani, MD, Christelle Charley Monaca, MD, PhD, Valérie Cochen De Cock, MD, PhD, Michel Boivin, PhD, Luigi Ferini-Strambi, MD, PhD, Giuseppe Plazzi, MD, PhD, Elena Antelmi, MD, Peter Young, MD, Anna Heidbreder, MD, Thomas R. Barber, MA, MBBS, MRCP, Samuel G. Evetts, BSc Hons, MSc, Michal Rolinski, BM BCh, BA Hons, MRCP, Patrick A. Dion, PhD, Alex Desautels, MD, PhD, Jean-François Gagnon, PhD, Nicolas Dupré, MD, MSc, Ronald B. Postuma, MD, MSc, Guy A. Rouleau, MD, PhD

PII: S0197-4580(16)30242-1

DOI: 10.1016/j.neurobiolaging.2016.10.002

Reference: NBA 9741

To appear in: *Neurobiology of Aging*

Received Date: 18 August 2016

Revised Date: 22 August 2016

Accepted Date: 1 October 2016

Please cite this article as: Gan-Or, Z., Montplaisir, J.Y., Ross, J.P., Poirier, J., Warby, S.C., Arnulf, I., Strong, S., Dauvilliers, Y., Leblond, C.S., Hu, M.T.M., Högl, B., Stefani, A., Monaca, C.C., De Cock, V.C., Boivin, M., Ferini-Strambi, L., Plazzi, G., Antelmi, E., Young, P., Heidbreder, A., Barber, T.R, Evetts, S.G., Rolinski, M., Dion, P.A., Desautels, A., Gagnon, J.-F., Dupré, N., Postuma, R.B., Rouleau, G.A., The dementia-associated *APOE* ε4 allele is not associated with REM sleep behavior disorder, *Neurobiology of Aging* (2016), doi: 10.1016/j.neurobiolaging.2016.10.002.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please

note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

The dementia-associated *APOE* ε4 allele is not associated with REM sleep behavior disorder

Ziv Gan-Or, MD, PhD,[a,b,c,] Jacques Y. Montplaisir, MD, PhD,[d,e,] Jay P. Ross, BSc,[b] Judes Poirier, PhD [f,g,] Simon C. Warby, PhD,[4,5,] Isabelle Arnulf, MD, PhD,[h,] Stephanie Strong, BSc,[a,] Yves Dauvilliers, MD, PhD,[i,] Claire S. Leblond, PhD,[1,b,] Michele T.M. Hu, MBBS, FRCP, PhD,[j,k,] Birgit Högl, MD,[l,] Ambra Stefani, MD,[l,] Christelle Charley Monaca, MD, PhD,[m,] Valérie Cochen De Cock, MD, PhD,[n,o,] Michel Boivin, PhD,[p,q,] Luigi Ferini-Strambi, MD, PhD,[r,] Giuseppe Plazzi, MD, PhD,[s,t,] Elena Antelmi, MD,[s,] Peter Young, MD,[u,] Anna Heidbreder, MD,[u,] Thomas R Barber MA, MBBS, MRCP,[j,k,] Samuel G. Evetts BSc Hons, MSc,[j,k,] Michal Rolinski, BM BCh, BA Hons, MRCP,[j,k,] Patrick A. Dion, PhD,[a,c,] Alex Desautels, MD, PhD,[d,v,] Jean-François Gagnon, PhD,[d,w,] Nicolas Dupré, MD, MSc,[x,] Ronald B. Postuma, MD, MSc,[c,y,] and Guy A. Rouleau, MD, PhD,[a,b,c].

Affiliations :
[a]Montreal Neurological Institute, McGill University, Montréal, QC, H3A 0G4, Canada, [b]Department of Human Genetics, McGill University, H3A 0G4, Montréal, QC, Canada, [c]Department of Neurology and neurosurgery, McGill University, Montréal, QC, H3A 0G4, Canada, [d]Centre d'Études Avancées en Médecine du Sommeil, Hôpital du Sacré-Cœur de Montréal, Montréal, QC, H4J 1C5, Canada, [e]Department of Psychiatry, Université de Montréal, Montréal, QC, H3T 1J4, Canada, [f]Department of Psychiatry, McGill University, Montréal, QC, H3A 0G4, Canada, [g]Douglas Mental Health University Institute, Montréal, QC, H4H 1R3, Canada, [h]Sleep Disorders Unit, Pitié Salpêtrière Hospital, Centre de Recherche de l'Institut du Cerveau et de la Moelle Epinière and Sorbonne Universities, UPMC Paris 6 univ, Paris, 75013, France, [i]Sleep Unit, National Reference Network for Narcolepsy, Department of Neurology Hôpital-Gui-de Chauliac, CHU Montpellier, INSERM U1061, Montpellier, 34000, France, [j]Oxford Parkinson's Disease Centre (OPDC), University of Oxford, Oxford, OX1 2JD, United Kingdom, [k]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX1 2JD, United Kingdom, [l]Sleep Disorders Clinic, Department of Neurology, Medical University of Innsbruck, Innsbruck, 6020, Austria, [m]University Lille north of France, Department of clinical neurophysiology and sleep center, CHU Lille, Lille, 59000, France, [n]Sleep and neurology unit, Beau Soleil Clinic, Montpellier, 34070, France, [o]EuroMov, University of Montpellier, Montpellier, 34095, France, [p]GRIP, École de psychologie, Université Laval, Québec city, QC, G1V 0A6, Canada, [q]Institute of Genetic, Neurobiological and Social Foundations of Child Development, Tomsk State University, Tomsk, 634050, Russia, [r]Department of Neurological Sciences, Università Vita-Salute San Raffaele, Milan, 20132, Italy, [s]Department of Biomedical and Neuromotor Sciences (DIBINEM), Alma Mater Studiorum, University of Bologna, Bologna, 40126, Italy, [t]IRCCS, Institute of Neurological Sciences of Bologna, Bologna, 40139, Italy, [u]Department of Sleep Medicine and Neuromuscular Disorders, University of Muenster, 48149, Germany, [v]Department of Neurosciences, Université de Montréal, Montréal, H3T 1J4, Canada, [w]Département de psychologie, Université du Québec à Montréal, Montréal, QC, H2L 2C4, Canada, [x]Faculté de Médecine, Université Laval, CHU de Québec (Enfant-Jésus), Québec, QC, G1J 1Z4, Canada, [y]Department of Neurology, Montreal General Hospital, Montréal, QC, H3G 1A4, Canada.

ACCEPTED MANUSCRIPT

Correspondence:

Ziv Gan-Or
Montreal Neurological Institute, McGill University
1033 Pine Avenue, West,
Ludmer Pavilion, room 327
Montreal, QC, H3A 1A1
Phone: +1-514-398-6821
e-mail: ziv.gan-or@mail.mcgill.ca

ACCEPTED MANUSCRIPT

Abstract: The current study aimed to examine whether the *APOE* ε4 allele, associated with dementia with Lewy bodies (DLB), and possibly with dementia in Parkinson's disease (PD), is also associated with idiopathic REM sleep behavior disorder (RBD). Two SNPs, rs429358 and rs7412, were genotyped in RBD patients (n=480) and in controls (n=823). *APOE* ε4 allele frequency was 0.14 among RBD patients and 0.13 among controls (OR=1.11, 95% CI 0.88-1.40, *p*=0.41). *APOE* ε4 allele frequencies were similar in those who converted to DLB (0.14) and those who converted to PD (0.12) or multiple system atrophy (0.14, *p*=1.0). The *APOE* ε4 allele is neither a risk factor for RBD nor it is associated with conversion from RBD to DLB or other synucleinopathies.

1. Introduction: Rapid eye movement (REM) sleep behavior disorder (RBD) is currently the strongest clinical prodromal feature preceding the development of an overt synucleinopathy, including Parkinson's disease (PD), dementia with Lewy bodies (DLB) or multiple system atrophy (MSA) (Iranzo, et al., 2014). One of the strongest genetic factors associated with DLB is the *APOE* epsilon4 (ε4) allele (Pickering-Brown, et al., 1994), and PD patients who carry this allele may be at increased risk for developing dementia. Since both RBD and the *APOE* ε4 allele are possibly associated with DLB, and with dementia in PD patients, we aimed to examine whether the *APOE* ε4 allele is associated with RBD and conversion to DLB. See Supplementary file for detailed introduction and full list of references.

2. Methods: The study population included idiopathic RBD patients (n=480) and controls (n=823) of European ancestry. RBD patients were diagnosed using clinical interview and polysomnography according to the ICSD-2 (International Classification of Sleep Disorders, version 2) criteria. The control group was composed of 253 elderly controls (age 59.5±9.8 years, matched to the available age at onset (AAO) of RBD, n=307, age 59.2±11.5), 510 young controls (age 34.0±6.5 years), and additional 60 controls with no available data on age. All control groups had nearly identical frequencies of the *APOE* ε4 allele (0.13, 0.13 and 0.14, respectively), which allowed us to analyze all controls combined. All

individuals signed informed consent forms at enrollment, and the study protocols were approved by the respective institutional review boards. DNA was extracted using a standard salting-out protocol. Two single nucleotide polymorphisms (SNPs), rs429358 and rs7412, were genotyped using TaqMan SNP genotyping assays. Genotypes were called using the QuantStudio™ 7 Flex Real-Time PCR System and Software (v 1.0). Goodness of fit test with one degree of freedom was applied to look for deviation from the Hardy-Weinberg equilibrium (HWE) among the controls. Differences in *APOE* allele or carriage frequencies were analyzed using the Fisher's exact test, and differences in continuous variables were analyzed using t-test. A logistic regression model with age and sex as covariates was also applied. All statistical analysis was done using SPSS statistics V.23 (IBM Inc.). Detailed methods can be found in the supplementary file.

3. Results: The allele frequency of *APOE* ε4 was 0.14 among RBD patients and 0.13 among controls (OR=1.11, 95% CI 0.88-1.40, p=0.41). Overall, 25.8% of RBD patients carried at least one *APOE* ε4 compared to 23.0% among controls (p=0.25, Fisher's exact test), and there were more homozygous carriers of the *APOE* ε4 allele among controls (3.2%) as compared to RBD patients (2.7%). Logistic regression model adjusted for age and sex also demonstrated lack of association between *APOE* ε4 allele carriage and risk for RBD (OR = 1.25, 95% CI 0.87-1.79, p=0.23). There was no difference in AAO when comparing carriers (n=88) and non-carriers (n=219) of the *APOE* ε4 allele (59.1 ± 8.4 vs. 59.3 ± 12.6 years, respectively, p=0.92, t-test). A total of 140 RBD patients (29.2%) were reported to have converted to either PD (n=98, 70% of the converters), dementia/DLB (n=28, 20%) or MSA (n=14, 10%). The carrier frequencies of one or more *APOE* ε4 in these groups were similar; 23.5%, 25.0% and 28.6%, respectively (p=0.91), and the allele frequencies were 0.12, 0.14 and 0.14 (p=1.0). The *APOE* ε4 allele frequency among those that did not convert was slightly higher, 0.15 (Table 1), with a total of 26.5% carriers of at least one *APOE* ε4 allele, compared to 24.3% among those who converted (p=0.65). More detailed results can be found in the supplementary file.

4. Discussion: Although RBD is a strong risk factor for developing DLB, and although DLB was reported to be associated with the *APOE* ε4 allele, our results demonstrate lack of association between the *APOE* ε4 allele and RBD or its age at onset. These and previous results further suggest that RBD may have a distinct genetic background; it is associated with *GBA* mutations (Gan-Or, et al., 2015b), but unlike PD it is not associated with *LRRK2* mutations (Fernandez-Santiago, et al., 2016), and unlike DLB it is not associated with the *APOE* ε4 allele. Thus far, *GBA*, *SCARB2*, and potentially *SNCA* (Gan-Or, et al., 2015a) overlap between RBD, PD and DLB (Supplementary Figure 1, see Supplementary file). Whether RBD has additional, unique genetic factors that were not identified in PD or DLB cohorts is still to be determined. Our current study identified similar frequencies of *APOE* ε4 allele in those who progressed to PD, DLB and MSA, suggesting that *APOE* alleles do not affect the type of subsequent synucleinopathy. Our study has some limitations, and a more detailed discussion including full list of references can be found in the supplementary file. Our results support a distinct genetic background for RBD-associated neurodegeneration, probably suggesting a specific genetic association with synucleinopathy rather than tauopathy/amyloidopathy.

References:

Fernandez-Santiago, R., Iranzo, A., Gaig, C., Serradell, M., Fernandez, M., Tolosa, E., Santamaria, J., Ezquerra, M. 2016. Absence of LRRK2 mutations in a cohort of patients with idiopathic REM sleep behavior disorder. Neurology 86(11), 1072-3. doi:10.1212/WNL.0000000000002304.

Gan-Or, Z., Girard, S.L., Noreau, A., Leblond, C.S., Gagnon, J.F., Arnulf, I., Mirarchi, C., Dauvilliers, Y., Desautels, A., Mitterling, T., Cochen De Cock, V., Frauscher, B., Monaca, C., Hogl, B., Dion, P.A., Postuma, R.B., Montplaisir, J.Y., Rouleau, G.A. 2015a. Parkinson's Disease Genetic Loci in Rapid Eye Movement Sleep Behavior Disorder. J Mol Neurosci 56(3), 617-22. doi:10.1007/s12031-015-0569-7.

Gan-Or, Z., Mirelman, A., Postuma, R.B., Arnulf, I., Bar-Shira, A., Dauvilliers, Y., Desautels, A., Gagnon, J.F., Leblond, C.S., Frauscher, B., Alcalay, R.N., Saunders-Pullman, R., Bressman, S.B., Marder, K., Monaca, C., Hogl, B., Orr-Urtreger, A., Dion, P.A., Montplaisir, J.Y., Giladi, N., Rouleau, G.A. 2015b. GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. Ann Clin Transl Neurol 2(9), 941-5. doi:10.1002/acn3.228.

Iranzo, A., Fernandez-Arcos, A., Tolosa, E., Serradell, M., Molinuevo, J.L., Valldeoriola, F., Gelpi, E., Vilaseca, I., Sanchez-Valle, R., Llado, A., Gaig, C., Santamaria, J. 2014. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 9(2), e89741. doi:10.1371/journal.pone.0089741.

Pickering-Brown, S.M., Mann, D.M., Bourke, J.P., Roberts, D.A., Balderson, D., Burns, A., Byrne, J., Owen, F. 1994. Apolipoprotein E4 and Alzheimer's disease pathology in Lewy body disease and in other beta-amyloid-forming diseases. Lancet 343(8906), 1155.

Disclosure statement

ZGO received consultation fees from Sanofi/Genzyme. JYM reports grants from Merck, GlaxoSmithKline, received speaking honoraria from Valeant Pharmaceutical, and Otsuka Pharmaceutical, serves on the advisory boards of Sanofi-Aventis, Servier, Merck, Jazz Pharma, Valeant Pharma, Impax Laboratories, Glaxo-SmithKline, UCB Canada, received consultancy fees from Otsuka Pharma, and Valeant Pharma. JPR reports no conflict of interests. JP reports no conflict of interests. SCW received honoraria from Pfizer, Bristol-Myers Squibb, SmithKline Beecham and Eli Lilly. IA received speaker honoraria form UCB Pharma. SS reports no conflict of interests. YD is on the advisory board and received travel and consultancy fees from UCB Phrma, bioprojet, and Jazz Pharma. CSL reports no conflict of interests. MTH reports no conflict of interests. BH received grant from UCB, speaker honoraria from UCB, Otsuka, Abbvie, Lundbeck, Lilly, Mundipharma. Serving on advisory boards or consulting for Mundipharma, Axovant. Received travel support from Habel Medizintechnik, Vivisol. AS reports no conflict of interests. CCM received fees for serving on advisory board of UCB pharma, lecture fees from UCB Pharma, Orkyn. VCD received funding from Orkyn, LVL medical, Teva and UCB. MB reports no conflict of interests. LFS reports no conflict of interests. GP served on the advisory board of UCB pharma, Jazz pharmaceuticals and Bioproject. EA reports no conflict of interests. PY received honoraria for speakers bureaus by Sanofi Genzyme, Biomarin, UCB pharma, Medice, ResMed and Heinen und Loewenstein. Member of advisory boards for Sanofi Genzyme, Biomarin, Vanda and Medice. AH received travel support Habel Medizintechnik, received lecture honoraria from UCB, Heinen und Löwenstein. TRB reports no conflict of interests. SGE reports no conflict of interests. MR reports no conflict of interests. PAD reports no conflict of interests. AD received research grants from Novartis pharma, Jazz Pharmaceuticals, Biron soins du sommeil. Received speaker honoraria from UCB and Paladin labs.

Acknowledgements

We would like to thank all the participants in the study. This work was funded by a grant to ZGO from the Michael J. Fox Foundation for Parkinson's research. Part of this work was funded by an interface grant to IA from INSERM. The French DNA collection was promoted by the Association pour le Développement et l'Organisation de la Recherche en Pneumologie et sur le Sommeil (ADOREPS), project PARAGEN, PI Isabelle Arnulf. The Oxford Discovery cohort was funded by the Monument Trust Discovery Award from Parkinson's UK and supported by the National Institute for Health Research (NIHR), Oxford Biomedical Research Centre based at Oxford University Hospitals, NHS Trust, University of Oxford, and the Dementias and Neurodegenerative Diseases Research Network (DeNDRoN). Part of this work was funded by the Weston Brain Institute (grants to JYM and JP) and the J.L. Levesque Foundation (grant to JP). Part of this work was funded by grants to PY from the Lowensteinstiftung and the German Ministry of Education and Science (BMBF). ZGO is supported by a postdoctoral fellowship from the CIHR. JFG holds a Canada Research Chair on Cognitive Decline in Pathological Aging. GAR holds a Canada Research Chair in Genetics of the Nervous System and the Wilder Penfield Chair in Neurosciences. We thank Cynthia Bourassa, Sandra Laurent, Helene Catoire, Pascale Hince and Vessela Zaharieva for their assistance.

ACCEPTED MANUSCRIPT

Table 1. *APOE* haplotypes in individuals with RBD and controls

APOE	**ε2/ε2 n, (%)**	**ε2/ε3 n, (%)**	**ε3/ε3 n, (%)**	**ε2/ε4 n, (%)**	**ε3/ε4 n, (%)**	**ε4/ε4 n, (%)**	**Total carriers of ε4, n (%)**	**ε4 allele frequency**
RBD patients, n=480	4 (0.8)	51 (10.6)	301 (62.7)	4 (0.8)	107 (22.3)	13 (2.7)	124 (25.8)	0.14
RBD converted to synucleinopathy[a], n=140	3 (2.1)	12 (8.6)	91 (65.0)	1 (0.7)	32 (22.9)	1 (0.7)	34 (24.3)	0.13
RBD not converted to synucleinopathy, n=340	1 (0.3)	39 (11.5)	210 (61.8)	3 (0.9)	75 (22.1)	12 (3.5)	90 (26.5)	0.15
Controls, n=823	5 (0.6)	111 (13.5)	518 (62.9)	14 (1.7)	149 (18.1)	26 (3.2)	189 (23.0)	0.13

n, number; RBD, REM sleep behavior disorder

[a] PD, dementia/DLB or MSA

ACCEPTED MANUSCRIPT